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EXAMINER	
MCKELVEY,J	
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/366,083	Applicant(s) Pomerantz et al.
	Examiner Terry A. McKelvey	Group Art Unit 1636

X Responsive to communication(s) filed on *5/13/99*.

X This action is **FINAL**.

Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

X Claim(s) *1-21, 24, 27-30, 34, 36, 40-70, and 72-98* is/are pending in the application.

Of the above, claim(s) *1-21, 24, 27-30, 34, and 36* is/are withdrawn from consideration.

Claim(s) _____ is/are allowed.

X Claim(s) *40-70 and 72-98* is/are rejected.

Claim(s) _____ is/are objected to.

Claims _____ are subject to restriction or election requirement.

Application Papers

See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

The drawing(s) filed on _____ is/are objected to by the Examiner.

The proposed drawing correction, filed on _____ is approved disapproved.

The specification is objected to by the Examiner.

The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

All Some* None of the CERTIFIED copies of the priority documents have been

received.

received in Application No. (Series Code/Serial Number) _____.

received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

Notice of References Cited, PTO-892

X Information Disclosure Statement(s), PTO-1449, Paper No(s). *25*

Interview Summary, PTO-413

Notice of Draftsperson's Patent Drawing Review, PTO-948

Notice of Informal Patent Application, PTO-152

--- *SEE OFFICE ACTION ON THE FOLLOWING PAGES* ---

DETAILED ACTION

Election/Restriction

Claims 1-21, 24, 27-30, 34, and 36 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b) as being drawn to a non-elected invention. Election was made **without** traverse in Paper No. 12.

This application contains claims 1-21, 24, 27-30, 34, and 36 drawn to an invention nonelected with traverse in Paper No. 12. A complete reply to the final rejection must include cancelation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> a A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a),

the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 40-70, 72, 89-92, 94-95, and 97 are rejected under 35 U.S.C. 103(a) as being unpatentable over Park et al (AW2) in view of Mitchel et al (S), Harrison (T) and Schultz (U). This rejection is maintained for reasons of record set forth in Paper No. 23, mailed 11/9/98 (and extended to new claims as necessitated by the applicant's amendment filed 5/13/99). Applicants' arguments filed 5/13/99 have been fully considered but they are not deemed to be persuasive.

Park et al teach a general strategy for designing proteins to recognize specific DNA-binding sites: this strategy is to select segments of proteins, each of which recognizes particular DNA segments and to stitch these segments together via a short peptide with a cysteine crosslink in a way compatible with each peptide being able to bind to its own DNA segment. This

technique creates a protein that recognizes the composite site (page 9094, column 1). This reference also teaches that use of the Gly-Gly-Cys linker is not essential in the design, that the cysteine can be replaced and a continuous approximately 70 amino-acid protein that should recognize a predictable site can be made (page 9095, column 2). The design is not limited to v-Jun. Any protein or other molecule that recognizes a specific DNA sequence by binding along the major groove could be a candidate. Many such cases are now known so that we already have a collection of available partial-binding sites that could be combined to form composite target-binding sites for designing binding proteins. Of course, the segments of these proteins should be designed so that the intramolecular interactions are not so strong as to compete with binding to the DNA (pages 9095-9096). Park et al also teach that the strategy is not limited to two arms and that they could have stitched together three, four, or more arms with appropriate linkers to design proteins that would recognize DNA sequences with 15, 20, or 25 bp (page 9095, column 2).

Park et al do not teach to specifically use the DNA-binding domains from distinct families of nucleic acid binding domains, use of specific types of domains such as zinc-finger domains.

Mitchell et al teach that different DNA binding transcription factors are composed of a surprising variety of usually separable DNA binding and transcriptional activation domains (page 372, column 2). This reference teaches zinc-finger domains, homeodomains, helix-turn-helix domains, steroid hormone receptor domains, leucine zipper domains, etc (pages 372-373). Various types of separable activation domains are also taught: acidic domains that can form an amphipathic alpha-helical structure, glutamine-rich domain, and proline-rich domain (pages 373-375).

Harrison teaches that many DNA-binding proteins recognize specific sites through small, discrete domains and that these domains can be interchanged between proteins, showing that they are independent folded units. Many different DNA-binding domains are taught, including HTH, homeodomains, different types of zinc-finger domains, steroid receptor DA binding domains, etc. Representative proteins having the domains, such as Zif268, etc are also taught and referenced (page 715).

Schultz teaches that enzymes can be created by adding or replacing entire binding or catalytic domains to generate hybrid enzymes with novel specificities. Selective fusion of nucleic acid-specific binding domains may produce sequence-specific DNA

or RNA cleaving enzymes (page 431, column 1). This reference teaches that tailor-made enzymes have applications in chemistry, biology and medicine.

It would have been obvious to one of skill in the art at the time the invention was made to use the various DNA binding domains, activation domains, and cleavage domains, including heterologous ones, taught by Mitchell et al, Harrison, and Schultz in the general strategy for designing proteins to recognize specific DNA-binding sites taught by Park et al because Park et al teach that it is within the ordinary skill in the art to stitch the DNA binding domains together from any proteins that recognize a specific DNA sequence by binding along the major groove, to recognize a composite site and Mitchell et al, Harrison, and Schultz teach such domains that can be functionally separated and recombined with other domains. One would have been motivated to do so for the expected benefit of creating a protein that recognizes the composite site, thereby increasing the specificity of the chimeric protein, as taught by Park et al, and creating hybrid enzymes with novel specificities that have applications in chemistry, biology and medicine as taught by Schultz. Absent evidence to the contrary, there would have been a reasonable expectation of success that the domains taught by

Mitchell et al and Harrison could be combined with each other to create a protein that recognizes a composite binding site as taught by Parks et al.

With regard to making a nucleic acid and vector comprising the nucleic acid which encodes the chimeric protein, it would have been obvious to do so because Parks et al teach that a continuous approximately 70 amino-acid protein that should recognize a predictable site can be made, instead of using a cysteine linker, and thus it would have been obvious to make a nucleic acid that encodes this protein and place the nucleic acid in a vector to express the protein, because such a way of making a mutated, recombinant protein is and was well known in the art.

With regard to the use of any specific domain or combinations of domains recited in the claims, it would have been obvious to make any of the recited combinations because the recited domains are all taught in the cited references or are and were well known in the art, and Parks et al teach that any combination of domains can be used, which would include heterologous ones.

With regard to the inclusion of an activation domain in the chimeric protein, it would have been obvious to do so because the cited references teach that the activation domain are separate

from the DNA binding domains and thus can be included. One would have been motivated to do so for the expected benefit of making a transcriptional activation protein that binds to a more specific composite site, as taught by Parks et al.

With regard to separating the domains by one or more amino acids in the chimeric protein, it would have been obvious to do so because Parks et al teach that the domains can be separated by a linker.

With regard to including an additional (third) nucleic acid binding domain, it would have been obvious because Park et al teach that more domains can be added, resulting in binding to a larger composite DNA binding site.

Response to Arguments

The applicant argues that the cited references fail to provide any motivation to combine the references that would be within the skill in the art at the time the application was filed.

The applicant's argument is not persuasive for the following reasons. In response to applicant's argument that there is no motivation to combine the references, the examiner recognizes that obviousness can only be established by combining or

modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the applicant failed to address the motivation that was clearly stated in the rejection set forth in the previous Office Action: "One would have been motivated to do so for the expected benefit of creating a protein that recognizes the composite site, thereby increasing the specificity of the chimeric protein, as taught by Park et al, and creating hybrid enzymes with novel specificities that have applications in chemistry, biology and medicine as taught by Schultz." The whole purpose of the Park et al reference is to teach a general strategy for designing proteins to recognize specific DNA-binding sites by selecting segments of proteins, each of which recognizes particular DNA segments, and to stitch them together via a short peptide in a way compatible with each peptide being able to bind its own DNA segment, to create a protein which recognizes the composite site. Park et al also teach that use of the Gly-Gly-Cys linker is not essential in the design, that the cysteine can

be replaced and a continuous approximately 70 amino-acid protein that should recognize a predictable site can be made (page 9095, column 2). By teaching that a continuous protein can be made instead of linking two separate proteins, the reference thus would demonstrate to one of ordinary skill in the art that a single nucleic acid encoding the continuous protein could be made for the expected benefit of easily producing the chimeric protein by expression of the nucleic acid using routine methods that are and were very well known in the art. This reference alone provides very strong motivation to make chimeric DNA-binding proteins that bind to composite sequences by fusing two previously separate DNA binding domains together (and thus provides motivation to make nucleic acids to encode the chimeric proteins).

The applicant also argues that Park et al fail to provide any evidence that the combination of DNA binding domains from two different DNA binding domains or DNA binding domains that do not occur together in nature would bind to a composite binding site, and that none of the secondary references nor knowledge in the art cure the defect, and in fact none of the cited secondary references teach chimeric DNA binding proteins. Thus, a person of skill in the art would not find sufficient motivation to

combine the teachings of the references. In essence, this is also an argument that there would have been no reasonable expectation of success in making the combination, even if there was motivation to combine the teachings of the cited references. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Park et al was not relied upon by itself to provide evidence that the combination of DNA binding domains from two different DNA binding domains or DNA binding domains that do not occur together in nature would bind to a composite binding site. It was a based upon the combination of the references. First, Park et al shows that two separate DNA binding domains can be joined together by an amino acid linker to form a protein that recognizes the composite site. This reference specifically teaches that its teachings are not limited to being applicable to the one example set forth (which happens to use the same two DNA binding domains). Park et al teach that the design is not limited to v-Jun. Any protein or other molecule that recognizes a specific DNA sequence by binding along

the major groove could be a candidate. Many such cases are now known so that we already have a collection of available partial-binding sites that could be combined to form composite target-binding sites for designing binding proteins. Of course, the segments of these proteins should be designed so that the intramolecular interactions are not so strong as to compete with binding to the DNA (pages 9095-9096). These teachings clearly show that Park et al envisioned that the teachings of the reference could reasonably be applied to any two or more DNA binding domains, including heterologous ones. The example of the method taught by Park et al did not rely upon the natural formation of the homodimer to link the two DNA binding domains. Otherwise, the reference would not have taught that the method is generally applicable to any DNA binding proteins. The method was based upon a molecular model in which the linkage of two separate DNA binding domains to form a Y-shaped scissors grip that would bind to the composite site. See Figure 1. To one of ordinary skill in the art (which is extremely high in this technology, typically Ph.D. level with at least several years of additional experience), this model showing two separate DNA binding domains being linked together in a Y-shaped scissors grip in which the two domains are brought together without interfering with each

other, clearly would be applicable to any two DNA-binding domains, including heterologous ones. Park et al clearly teach that general applicability.

Second, the Park et al teaching that the strategy is not limited to two arms and that they could have stitched together three, four, or more arms with appropriate linkers to design proteins that would recognize DNA sequences with 15, 20, or 25 bp (page 9095, column 2) also clearly shows that they felt that it was well within their skill from the provided teachings to make chimeric proteins that have three or more DNA-binding domains. This teaching clearly shows that the Park et al teachings do not rely upon the two DNA-binding domains being identical and part of a homodimer in the natural protein (based upon the detailed v-jun example) because Park et al teach that larger constructs can be made (which naturally could not rely upon some aspect of homodimer formation in the natural protein because three or more DNA-binding domains are proposed to be put together in a single construct, something not present in v-jun).

Third, the teachings of the other cited references clearly further show that there would have been a reasonable expectation of success in applying the Park et al teachings to heterologous DNA binding domains because of the same general nature of DNA-

binding domains. For example, Mitchell et al teach that different DNA binding transcription factors are composed of a surprising variety of usually separable DNA binding and transcriptional activation domains (page 372, column 2). This reference teaches zinc-finger domains, homeodomains, helix-turn-helix domains, steroid hormone receptor domains, leucine zipper domains, etc (pages 372-373). Various types of separable activation domains are also taught: acidic domains that can form an amphipathic alpha-helical structure, glutamine-rich domain, and proline-rich domain (pages 373-375). Harrison teaches that many DNA-binding proteins recognize specific sites through small, discrete domains and that these domains can be interchanged between proteins, showing that they are independent folded units. [The underlining was added for instant emphasis.] As shown by the references, the fact that the DNA-binding domains of various transcription factors were known in the art to recognize specific sites through small, discrete, and thus separable domains, it would clearly demonstrate to one of skill in the art that they could be used in the general method taught by Park et al which depends on linking together two DNA-binding domains that recognize two different sites in way that does not interfere with their binding (in a scissors grip fashion), resulting in a

protein that binds to the composite site. Thus, there would have been a reasonable expectation of success in combining the references to result in the claimed invention because Park et al show that two DNA-binding domains can be stitched together in a scissor grip fashion to recognize a composite site, thus not relying upon formation of a homodimer. Because of the scissors grip model, Park et al teach that the method is generally applicable to any DNA binding protein of the major groove, which encompasses most if not all of the sequence-specific DNA binding factors. The other cited references show how discrete and easily separated DNA-binding domains are from the rest of the protein. Thus, to one of ordinary skill in the art, from the cited teachings, there clearly would have been a reasonable expectation of success in combining the references to result in the claimed invention.

The applicant also essentially argues that because the cited references, Park et al especially, did not actually teach the combination of DNA binding domains from two different DNA binding domains or of DNA binding domains which do not occur together or in the same order and/or with the same spacing as the protein in nature, and the applicants were first to demonstrate that the combination results in a composite DNA binding domain, there

would have been no reasonable expectation of success in making the combination prior to the applicant's teachings. This argument is not persuasive because the rejection is based upon 35 USC 103(a). Arguments drawn to the idea that because one of the references in the rejection did not teach the whole invention, there would not have been a reasonable expectation of success is an unpersuasive argument because it is essentially saying that no rejections based upon 35 USC 103(a) rejections are valid because ALL rejections based upon 35 USC 103(a) involve references which DO NOT teach the WHOLE invention. This idea is clearly erroneous. The rejection set forth above and in the previous Office Action clearly covers the required elements for the rejection showing that the invention would have been obvious under 35 USC 103(a). The reason why there would have been a reasonable expectation of success from combining the cited teachings in the references was set forth in the rejection and repeated in the instant arguments above. The applicant did not specifically address the cited basis for the reasonable expectation of success.

Finally, the applicant argues that the cited references fail to teach or suggest all the claim limitations, specifically, the nucleic acid encoding a chimeric DNA binding protein. Again, the

applicant's argument is not persuasive because the applicant has failed to address the basis of this limitation in the rejection set forth in the previous Office Action. The following is a copy of the paragraph in the previous rejection covering this limitation showing why it would have been obvious to make the claimed nucleic acid from the cited references:

" With regard to making a nucleic acid and vector comprising the nucleic acid which encodes the chimeric protein, it would have been obvious to do so because Parks et al teach that a continuous approximately 70 amino-acid protein that should recognize a predictable site can be made, instead of using a cysteine linker, and thus it would have been obvious to make a nucleic acid that encodes this protein and place the nucleic acid in a vector to express the protein, because such a way of making a mutated, recombinant protein is and was well known in the art." The creation of a nucleic acid to encode a protein of a particular amino acid sequence, including fusion proteins, is a technology that is over two decades old which is and was extremely well known in the art. It is the basis of the whole recombinant DNA technology upon which biotechnology is based. Once a reference teaches that a particular protein sequence should be made, the first thought one of ordinary skill in the

art has with regard to making the protein is that a nucleic acid encoding the protein should be made and expressed in a vector of choice. That is usually the only feasible way of making large quantities of a protein of a specific sequence. Therefore, the nucleic acid limitation would have been obvious to one of ordinary skill in the art from the teachings of the fusion protein suggested from the combination of the teachings of the cited references.

Therefore in light of the rejection set forth above and in the previous Office Action, the applicant's arguments, and the arguments set forth above, the claimed invention is still considered to have been obvious and the rejection under 35 USC 103(a) is maintained.

Claims 40-70 and 72-98 are rejected under 35 U.S.C. 103(a) as being unpatentable over Park et al (AW2), Mitchel et al (S), Harrison (T) and Schultz (U) as applied to claims 40-72 above, and further in view of Gossen et al (A). This rejection is maintained for reasons of record set forth in Paper No. 23, mailed 11/9/98 (and extended to new claims as necessitated by the applicant's amendment filed 5/13/99). Applicants' arguments

filed 5/13/99 have been fully considered but they are not deemed to be persuasive.

The teachings of Park et al (AW2), Mitchel et al (S), Harrison (T) and Schultz (U) are cited above and applied as before. These references do not specifically teach placing the nucleic acid encoding the chimeric protein into a vector in which the expression of the chimeric protein is under the control of a promoter permitting gene expression in eukaryotic cells, a kit comprising the nucleic acid encoding the chimeric protein and a gene operably linked to the composite binding site, use of the chimeric protein for modulating expression of a gene in a cell comprising modulating expression of the chimeric protein in a cell which includes a gene operably linked to the composite binding site, and a method of making a cell for use in the claimed expression method.

Gossen et al teach a nucleotide molecule coding for a chimeric transactivator fusion protein comprising a DNA binding domain (tet repressor binding domain) and a transactivation domain (such as VP16 of HSV). A negative system, comprising a repressor domain, is also taught (column 2). A second nucleic acid is taught coding for a heterologous protein which is operably linked to a tet operator (the binding site for the DNA

binding domain). A method to regulate gene expression by cultivating the eukaryotic cell comprising the nucleic acid vectors in a medium comprising tet is also taught, as is a kit comprising the nucleic acids (abstract; columns 1-3). A method of making such eukaryotic cells by transfecting the nucleic acids into the cells is taught (columns 3, 9). This reference also teaches that it is desired to create regulatory systems that do not rely on endogenous control elements (column 1).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to form a transcriptional regulatory system from the DNA encoding a chimeric transactivation protein made obvious by the teachings of Park et al (AW2), Mitchel et al (S), Harrison (T) and Schultz (U), using the method taught by Gossen et al because Gossen et al teach that it is within the ordinary skill in the art to make a nucleic acid vector that encodes a chimeric transactivator fusion protein (under the control of a promoter active in eukarytoic cells), make a nucleic acid encoding a heterologous protein operably linked to a regulator binding site that the chimeric protein binds to, place the nucleic acids in a eukaryotic cell, regulate the expression of the chimeric protein, thereby regulating expression of the heterologous protein, and the other cited

references teach a chimeric fusion transactivator protein that could be used to regulate the expression of genes in a similar fashion as that taught by Gossen et al. One would have been motivated to do so for the expected benefit of making regulatory systems that do not rely on endogenous control elements, the desirability of which is taught by Gossen et al. Absent evidence to the contrary, there would have been a reasonable expectation of success that the chimeric protein encoding DNA taught by the other cited references could be used to make a new, non-endogenous element regulatory system using the teachings of Gossen et al.

Response to Arguments

With regard to the instant rejection, the applicant essentially repeated the arguments set forth in the previous rejection above and stated that the Gossen reference does not cure the alleged defects in the rejection. Gossen et al was not relied upon for those teachings, but instead was used to show the obviousness of claims with additional limitations. The applicant did not argue those additional limitations. The applicant's arguments with regard to the alleged defects were addressed above and are equally applicable in the instant rejection. Therefore,

the applicant's arguments have already been fully addressed and thus the instant rejection under 35 USC 103(a) is maintained for the same reasons as the rejection set forth above.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

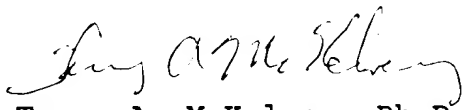
A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Certain papers related to this application may be submitted to Art Unit 1636 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone numbers for the Group are (703) 308-4242 and (703) 305-3014. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terry A. McKelvey whose telephone number is (703) 305-7213. The examiner can normally be reached on Monday through Friday, except for Wednesdays, from about 6:30 AM to about 5:00 PM. A phone message left at this number will be responded to as soon as possible (usually no later than 24 hours after receipt by the examiner).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. George Elliott, can be reached on (703) 308-4003.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.



Terry A. McKelvey, Ph.D.
Primary Examiner
Art Unit 1636

August 2, 1999